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COMPLETE SPECIFICATION

A Nutritionally Adequate, Non-Residual Dietary Composition for the reduction of the Intestinal Microflora Level

We, VIVONEX CORPORATION, a corporation duly organised and existing under the laws of the State of Delaware, U.S.A., of 867 West Dana Street, Mountain View, State of California 94040, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

This invention relates to dietary compositions.

It is known that the intestinal tract is normally infected with large amounts of various bacteria and in the treatment or management of certain untoward physiological conditions (diseased states) it is desirable substantially to reduce this level. For example, it is known that treatment of certain diseases caused by pathogenic bacteria in the intestinal tract requires a reduction of the level of these bacteria. Also, in preparing patients for surgery of the intestinal tract, it is particularly desirable to reduce the bacterial content of the intestines to reduce the danger of infection. Further, aside from the fact that certain bacteria are pathogens, many bacteria in the intestinal tract produce toxins, either as by products of their own metabolism or as a result of the action of these bacteria on the contents of the intestinal tract. It is known, for example, that certain bacteria act on nitrogenous components in the intestinal tract to produce ammonia. In severe liver disease, e.g. cirrhosis, where the body's ability to metabolize ammonia is hampered, it would be desirable to reduce the ammonia level by eliminating the bacteria that act on the nitrogenous material in the intestine to produce the ammonia.

Another application would be the reduction of gut microflora in clinical states which involve treatment with chemotherapeutic agents whose effective dosage level can be lowered by reducing the population level of intestinal microflora.

In the past, various attempts have been made to reduce the bacterial level in the intestine and these attempts have taken a variety of basic approaches. One approach is a physical elimination of the contents of the intestines. This has been accomplished generally by fasting which may also be taken together with enemas to physically flush out the intestinal track. Obviously, this is not a satisfactory approach in severely ill patients. Another approach has been through massive doses of antibiotics. However, this approach has not been particularly successful since prolonged use of antibiotics tends to result in the development of resistant strains of bacteria and, in addition, the antibiotic effect on the bacteria can enhance the growth of undesirable yeasts and molds.

Further, this approach cannot be practiced on patients who are sensitive to antibiotics.

However, it has been found that a substantial reduction of the number and type of intestinal microflora can be obtained by confining a subject to a nutritionally adequate nonresidual diet as a sole source of sustenance. The intestinal tract may then be infected with a controlled type of bacteria, such as *Lactobacillus*, in order to establish a new intestinal flora pattern. In addition to the lowering of the intestinal microflora as set forth above, such as in the preparation of the patient for intestinal surgery or to the lowering of the blood ammonia levels of the subject, it has also been found that desirable effects are produced in certain other medical situations. For example, a subject suffering from amoebic

dysentery can be fed the non-residual dietary compositions prepared according to this invention to reduce the intestinal microflora. Since the growth and replication of the amoeba depend upon the presence of the intestinal microflora, the elimination of such microflora also causes the elimination of the amoeba themselves. This approach to treatment of amoebic dysentery differs from the conventional practice of utilizing a substance that is toxic to the amoeba.

Certain bacterial species, such as *Streptococcus faecalis,* produce through their metabolic action on amino acids, a certain class of material known as pressor amines, which can cause an elevation in blood pressure. It has been found that administration of the non-residual dietary compositions whose preparation is described herein leads to a reduction in the blood pressure of normotensive and hypertensive subjects and that this decrease in blood pressure occurs at the same time as the reduction in gut microflora.

The use of the dietary compositions according to the invention, the preparation of which is to be described hereinafter, will cause a reduction in the high probability of secondary infection concomitant with treatments involving massive doses of ionizing radiation or administration of certain chemotherapeutic agents. It is known that ionizing radiation and certain chemotherapeutic agents, e.g. nitrogen mustard derivatives, increase the susceptability to infection by such means as promoting ulceration of the digestive tract, or increasing the permeability of the intestinal wall to such an extent that bacteria may pass through the wall and into the abdominal cavity causing infections such as peritonitis. By administration of the dietary compositions according to the invention, thereby reducing the intestinal microflora prior to and during the radiation or chemotherapeutic regimen and for a reasonable period following completion of treatment, the danger of infection which arises from the administration of such agents can be substantially reduced.

According to the present invention there is provided a nutritionally-adequate, non-residual dietary composition for mixing with water prior to consumption, which composition comprises a water-soluble component and a fat-soluble component; the water-soluble component comprising one or more water-soluble carbohydrates together with vitamins, minerals and, as sources of nitrogen, amino acids, amino acid derivatives, protein hydrolysates or mixtures thereof, the carbohydrate providing the major proportion (calculated as dry solid weight) of the said composition; and the fat-soluble component comprising one or more fat-soluble vitamins together with a small but nutritionally-adequate amount of fat, fat substitute or fatty acid or mixture thereof; the ingredients of the said composition being such as to provide in use a nutritionally-adequate diet serving to reduce intestinal microflora level.

The water-soluble component of the compositions according to the invention advantageously includes a non-toxic emulsifier. The compositions can then be mixed with water to produce an emulsion prior to consumption.

For a better understanding of the present invention reference is made to the accompanying drawings wherein:

Figure 1 shows a graphic representation of the effect of the non-residual diet regimen on the intestinal microfloral pattern of a typical subject and

Figure 2 shows a graph of the corresponding levels of intestinal *Corynebacteriaceae* and blood ammonia exhibited by the subject of Example 3.

As used herein, the term "non-residual dietary composition" refers to a substantially bulk-free diet formulation capable of maintaining normal physiological function. Subjects fed such non-residual dietary compositions for extended periods of time exhibit no deleterious side effects and maintain normal physiological function. The non-residual dietary compositions according to the invention may be prepared in various forms, such as solids, powders, slurries, solutions or emulsions. Emulsions are preferred forms and advantageously they may be prepared from an aqueous solution of the water soluble components the fat and fat soluble components being added to form the aqueous emulsions. In the formation of emulsions, non-toxic emulsifiers are used such as, for example, polyoxyethylene sorbitan monooleate. Suitable artificial flavoring and food colouring may be employed, if desired, to improve the appeal of the compositions for human consumption.

The relative amounts of the various components of the dietary compositions can be varied within fairly wide limits. The carbohydrate, vitamin, and mineral components, of course, should be selected so as to supply adequate calorific value and to adequately meet the necessary daily minimum requirements for the vitamin and mineral components, respectively.

In general, glucose is the preferred carbohydrate for use in the compositions according to the present invention but other carbohydrates may also be used, for example in the form of a derivative thereof such as glucono - δ - lactone. Again, a wide variety of mineral may be used in these compositions and may for example, include salts containing ions such as alkali metal ions e.g. sodium and potassium, alkali earth metal cations e.g. magnesium, calcium and zinc or ions such as ammonia, manganous, cobaltous or ferrous. The vitamins used in the formulation of the compositions according to the invention include both water soluble and fat soluble types.

The water soluble vitamins may include, for example, thiamine.HCl, riboflavin, pyridoxin.HCl, niacinamide, inositol, d-Ca pantothenate, d-biotin, folic acid, ascorbic acid, cyanocobalamin, p-aminobenzoic acid, choline bitartrate and the fat soluble vitamins may include, for example, vitamin A as its acetate, vitamin D, α-tocopherol as its acetate and menadione.

The fat component which may be a fat, for example, a mono, di or triglyceride, or a simple fatty acid ester, for example ethyl linoleate, or a fatty acid should be maintained at a level sufficient to meet the needs of normal physiological function. It has been observed that a level of essential fat as low as 0.2% by weight of solids in otherwise adequate dietary compositions is sufficient to maintain normal health over a period of time.

The nitrogen source may, for example, comprise both essential and non-essential nitrogen sources and these are supplied either as protein hydrolysates or as free amino acids or suitable derivatives thereof such as amides, esters, or salts of amino acids in appropriate balance and proportion to meet nutritional requirements. Because of a strong interdependency between required level of a given amino acid and the level of one or more of the other amino acids present in a diet, it is not practicable to establish a range of levels for each of the amino acids. Advantageously, the amino acids and derivatives thereof employed in the dietary compositions according to the invention comprise a mixture of the laevo form of lysine monohydrochloride, leucine, isoleucine, valine, phenylalanine, arginine monohydrochloride, histidine monohydrochloride monohydrate, alanine, aspartic acid, threonine, proline, glycine, serine, tyrosine ethyl ester monohydrochloride, glutamine, methionine, or tryptophan. However, the ratio of levels of amino acids either in free form or as derivatives thereof in the dietary compositions should approximate to those of a high-quality protein such as meat, eggs, or milk, for example, even though subject to broad variations without being detrimental to health. The amino acid content of such materials is set forth in M. L. Orr and B. J. Watts "Amino Acid Content of Foods" Home Economics Research Report No. 4, Agricultural Research Service, U.S. Department of Agriculture, December, 1957, available from the Superintendent of Documents, U.S. Government Printing Office, and which can serve as a useful guide in the formulation of the compositions according to this invention. A useful guide in determining minimum amino acid requirements to formulate diets other than those specifically disclosed herein is found in the "Protein Requirements" report of the FAO Committee, Food and Agricultural Organization of the United Nations, Rome, Italy, 24F, 31 October, 1957, available from Columbia University Press. Three representative diet formulations according to this invention are set forth in the following Tables I, II, and III. The calorific values of such diets vary with the concentration of various nutrients that compose the dietary regime. Convenient calorific levels have been found to range from about 0.5 to 2.5 calories per milliliter when the diet is provided in liquid form.

TABLE I

Diet Formulation I

Amino Acids

L-Lysine HCl	3.58 g	Sodium L-Aspartate	6.40 g
L-Leucine	3.83 g	L-Threonine	2.42 g
L-Isoleucine	2.42 g	L-Proline	10.33 g
L-Valine	2.67 g	Glycine	1.67 g
L-Phenylalanine	1.75 g	L-Serine	5.33 g
L-Arginine.HCl	2.58 g	L-Tyrosine ethyl ester HCl	6.83 g
L-Histidine.HCl.H_2O	1.58 g	L-Tryptophan	0.75 g
L-Methionine	1.75 g	L-Glutamine	9.07 g
L-Alanine	2.58 g	L-Cysteine ethyl ester.HCl	0.92 g

TABLE I—*Continued*

Water-Soluble Vitamins

Thiamine.HCl	1.00 mg	d-Biotin	0.83 mg
Riboflavin	1.50 mg	Folic acid	1.67 mg
Pyridoxin.HCl	1.67 mg	Ascorbic acid	62.50 mg
Niacinamide	10.00 mg	Cyanocobalamin	1.67 mcg
Inositol	0.83 mg	p-Aminobenzoic acid	416.56 mg
d-Ca pantothenate	8.33 mg	Choline bitartrate	231,25 mg

Salts

Potassium iodide	0.25 mg	Ammonium molybdate.$4H_2O$	0.42 mg
Manganous acetate.$4H_2O$	18.30 mg	Potassium hydroxide	3.97 g
Zinc benzoate	2.82 mg	Magnesium oxide	0.38 g
Cupric Acetate.H_2O	2.50 mg	Sodium chloride	4.77 g*
Cobaltous acetate—$4H_2O$	1.67 mg	Ferrous gluconate	0.83 g
Sodium glycerophosphate	5.23 g	Calcium chloride—H_2O	2.44 g*
or		Sodium benzoate	1.00 g
Monocalcium fructose-1:6-diphosphate	7.07 to 10.90 g*		

Carbohydrates

Glucose	530 to 570 g	Glucono-δ-lactone	17.20 g

Fats and Fat-Soluble Vitamins

Ethyl linoleate	2.000 g	α-Tocopherol acetate	57.29 mg
Vitamin A acetate	3.640 mg	Menadione	4.58 mg
Vitamin D	0.057 mg		

Flavoring

Synthetic flavoring agents and distilled water are added in amounts compatible with optimal palatability.

* When monocalcium fructose -1:6-diphosphate is employed the calciumchloride and sodium glycerophosphate are deleted from the formulation and the sodium chloride is appropriately adjusted upward.

TABLE II

Diet Formulation II

Amino Acids

L-Lysine.HCl	3.58 g	L-Aspartic acid	5.50 g
L-Leucine	3.83 g	L-Threonine	2.42 g
L-Isoleucine	2.42 g	L-Proline	3.42 g
L-Valine	2.67 g	Glycine	4.20 g
L-Phenylalanine	2.75 g	L-Serine	1.78 g
L-Arginine.HCl	5.70 g	L-Tyrosine ethyl ester.HCl	4.10 g
L-Histidine.HCl.H_2O	1.58 g	L-Tryptophan	0.75 g
L-Methionine	2.48 g	L-Glutamine	9.15 g
L-Alanine	2.58 g		

Vitamins

Thiamine.HCl	1.00 mg	d-Biotin	0.83 mg
Riboflavin	1.50 mg	Folic acid	1.67 mg
Pyridoxin.HCl	1.67 mg	Ascorbic acid	62.50 mg
Niacinamid	10.00 mg	Cyanocobalamin	1.67 mcg
Inositol	0.83 mg	p-Aminobenzoic acid	416.56 mg
d-Ca pantothenate	8.33 mg	Choline bitartrate	231.25 mg

Salts

Potassium iodide	0.25 mg	Ammonium molybdate.$4H_2O$	0.42 mg
Manganous acetate.$4H_2O$	18.30 mg	Potassium hydroxide	4.00 g
Zinc chloride	1.25 mg	Magnesium oxide	0.38 g
Cupric acetate.H_2O	2.50 mg	Sodium hydroxide	1.68 g
Cobaltous acetate.$4H_2O$	1.67 mg	Ferrous ammonium sulfate.$6H_2O$	0.68 g
Sodium glycerophosphate	5.23 g	Calcium chloride.$2H_2O$	2.44 g
Potassium sorbate	1.00 g	Sodium chloride	5.35 g

TABLE II—*Continued*

Carbohydrates

Glucose	570 g	Glucono-δ-lactone	17.20 g

Fats and Fat-Soluble Vitamins

Ethyl linoleate	2.000 g	α-Tocopherol acetate	57.29 mg
Vitamin A acetate	3.640 mg	Menadione	4.58 mg
Vitamin D	0.057 mg		

Flavoring

Synthetic flavoring agents and distilled water are added in amounts compatible with optimal palatability.

TABLE III

Base Diet Composition

Amino Acids

L-Lysine.HCl	3.58 g	L-Aspartic acid	5.50 g
L-Leucine	3.83 g	L-Threonine	2.42 g
L-Isoleucine	2.42 g	L-Proline	3.42 g
L-Valine	2.67 g	Glycine	4.20 g
L-Phenylaline	2.75 g	L-Serine	1.77 g
L-Arginine.HCl	5.70 g	L-Tyrosine ethyl ester.HCl	4.10 g
L-Histidine HCl.H_2O	1.58 g	L-Glutamine	9.07 g
L-Alanine	2.58 g	L-Methionine	1.75 g
		L-Tryptophan	0.75 g

Vitamins

Thiamine.HCl	1.20 mg	d-Biotin	0.30 mg
Riboflavin	1.70 mg	Folic acid	0.10 mg
Pyridoxin.HCl	1.67 mg	Ascorbic acid	80.00 mg
Niacinamide	10.00 mg	Cyanocobalamin	15.00 mg
Inositol	0.83 mg	p-Aminobenzoic acid	416.56 mg
d-Ca pantothenate	14.00 mg	Choline bitartrate	231.25 mg
Vitamin A acetate	5,000.00 units	*α-Tocopherol acetate	30.00 mg
Vitamin D_2—D_3	400.00 units	Menadione	60.00 mg

* U.S.P.

TABLE III—*Continued*

Salts

Potassium iodide	0.15 mg	Zinc chloride	1.20 mg
Manganous acetate.$4H_2O$	18.33 mg	Potassium hydroxide	3.97 g
Cupric acetate.H_2O	2.50 mg	Magnesium oxide	0.37 g
Sodium glycerophosphate	5.23 g	Sodium hydroxide	1.67 g
Sodium chloride	5.35 g	Calcium chloride.$2H_2O$	2.44 g
Ferrous ammonium sulphate	0.682 mg		

Carbohydrates

Glucose	555.0 g	Glucono-δ-lactone	17.20 g

Fats

Ethyl linoleate	2.00 g

Emulsifier

Polyoxyethylene sorbitan monooleate	2.00 g

Flavoring

Synthetic flavoring agents and distilled water are added in amounts compatible with optimal palatability.

If desired, the baseline intestinal microfloral pattern of a subject could first be determined by the standard becteriological techniques to provide a determination of not only the types of bacteria present, but also the relative amounts of the respective bacteria. The subject is confined to the non-residual dietary composition according to the invention as the sole source of sustenance, and maintained on the composition until a drastic reduction of intestinal microflora is achieved. Typically, total microflora population per gram of wet feces will be reduced within a period of about two weeks from between about 1×10^{8}—1×10^{11} to between about 1×10^{2}—1×10^{3}, e.g., the total population will be reduced by a factor of between about 1×10^{5}—1×10^{9}. In addition, the dramatic reduction in amount of fecal matter present in the lower bowel will effect a further reduction of between 5 and 10 fold in the total bacterial population.

When the bacterial level has been reduced to the desired level, the subject is maintained on the non-residual dietary composition regimen for the period of time required to produce the desired therapeutic effect. The subject may then be returned to natural foodstuffs.

According to another practice, the subject's intestinal tract can be infected with a controlled bacterial type, e.g., *Lactobacillus* by administration to the subject of an appropriate source of the desired bacterial type, or by feeding selected foodstuffs such as diary products, e.g. yogurt, which tend to mediate the growth of certain bacterial types.

It has been found that a substantial reduction in all Gram positive bacterial with the exception of certain cocci occurs rapidly, i.e., within 5 days, following the start of administration of the non-residual dietary composition and, further, that all bacterial species are substantially reduced within a period of about 2 weeks.

Figure 1 illustrates the effect of the non-residual dietary compositions prepared according to the invention on the intestinal microflora pattern of a typical subject and also illustrates the effect of a return to natural foodstuffs on the intestinal microflora pattern. As can be seen, the regimen typically eliminates all types of intestinal microflora except *E. coli*, *Bacteroides*, and *Enterococci* and produces a marked reduction in the level of these bacteria. Upon return to natural foodstuffs, the level of these bacteria tends to increase and, typically, a microfloral pattern similar to the pattern prior to the non-residual diet regimen tends to become established.

The following examples are illustrative of the manner in which the non-residual dietary compositions according to the present inventoin may be used.

EXAMPLE 1.

Subjects confined to the non-residual dietary composition of Table II showed changes in intestinal flora with time as shown in Table IV. As can be seen from Table IV, the bacterial floral population of each subject showed a dramatic reduction in number and variety, with the more fastidious microorganisms, e.g., *Lactobacilli, Staph. aureus, Clostridia*, etc. disappearing most rapidly and the less fastidious microorganisms or those indigenous to the lower bowel, e.g., *E. coli, Bacteroides, Enterococci*, diminishing more slowly.

As used herein, a "fastidious microorganism" is one which has a limited spectrum of dietary nutrient and environmental, e.g., pH, mineral concentration, etc., requirements for maintenance and replication.

In all four subjects, after remaining on the diet for extended periods of time, the intestinal floral pattern consisted only of *E. coli, Bacteroides*, and cocci and the number of each of these types per gram of wet feces had decreased by several orders of magnitude from that originally exhibited by each subject. Since the stool reservoir of each individual was also decreased by a conservative factor of a least 5 fold, the reduction in the total amount of bacteria present in the intestines was actually much greater than is revealed by the bacteria density figures given in table IV.

TABLE IV

Intestinal Microflora Population (Log Count/Gm Wet Feces)

Intestinal Microflora Species	Subject A					Subject B					Subject C				Subject D			
	0*	6+	8	14	17	0	6	8	13	15	0	12	14	15	0	5	7	9
E. Coli	4	2	1	1	2	6	7	6	2	2	5	5	2	2	4	4	2	1
Lactobacilli	n	n	n	n	n	6	n	n	n	n	4	n	n	n	3	n	n	n
Enterococci	4	3	4	2	2	5	n	2	2	2	5	3	2	2	5	3	3	2
Streptococci	n	n	n	n	n	4	n	n	n	n	4	n	n	n	2	n	1	n
Bacteroides	5	5	4	3	3	9	6	2	3	3	4	5	2	4	7	6	4	3
Clostridia	2	n	n	n	n	6	n	n	n	n	n	n	n	n	n	n	n	n
B. subtilis	2	n	n	n	n	n	n	2	n	n	2	n	n	n	2	n	n	n
Yeast-like fungi	1	n	n	n	n	4	n	n	n	n	n	n	n	n	1	n	n	n
Cumulative caloric intake of diet to time of fecal sample (thousands of calories)	0	12.	14.	22.	25.	0	7.	11.	16.	18.	0	21.	23.	24.	0	8.	11.	12.

* Baseline.

+ Days on non-residual diet as sole source of sustenance.

Note: Symbol "n" denotes no detectable amounts of the microflora species.

EXAMPLE 2.

Two subjects were confined to the non-residual dietary compositions of Table II as a sole source of sustenance for a period of four weeks. The amino acids, water soluble vitamins, minerals, and carbohydrates were administered in the form of an aqueous solution whereas the fats and fat soluble vitamins were administered as a separate daily supplement. The base-line intestinal flora pattern of subject 1 was as follows:

E. coli	5.0×10^6	*Clostridia*	1.3×10^4
Aerobacter	1.0×10^6	Yeast-like fungi	1.0×10^3
Staphylococcus aureus	1.6×10^3	*Enterococci*	1.5×10^4
Lactobacilli	5.0×10^5	*Streptococci* (hemolytic)	1.0×10^2
Bacteroides	2.0×10^5	Molds	2.0×10^1

All of the above values being in terms of number of the particular microbe per gram of wet feces. At the end of the fourth week, the intestinal flora pattern was as follows:

E. coli	4.0×10^3
Bacteroides	8.0×10^3
Yeast-like fungi	1.8×10^4

No other microorganisms were detectable.

The second subject had a base-line pattern per gram of wet feces as follows:

E. coli	1.1×10^5
Lactobacilli	6.0×10^4
Bacteroides	5.0×10^6
Clostridia	5.0×10^3
B. subtilis	1.0×10^5
Enterococci	1.0×10^3

At the end of the four week period, the intestinal flora pattern showed only yeast-like fungi in amount of 8×10^1. No other microorganisms were detectable.

The two subjects described in detail above were part of a study of seventeen subjects. An examination of the data obtained by bacteriological analysis of the fecal samples of a group of seventeen subjects who were maintained on the diet for a period of 3 to 10 weeks led to the following observations. The stools of all seventeen subjects were characterized by the total absence of detectable numbers of Gram positive bacteria, except cocci. A separate experiment with a different group of subjects showed that their stools were completely devoid of Gram positive microorganisms other than cocci within 4 days after changing from natural foodstuffs to the non-residual dietary compositions. Seven of the previously identified seventeen subjects who had been maintained on the diet for periods of time varying from 3 to 10 weeks delivered fecal samples showing a complete absence of *E. coli*. The feces of these seven subjects contained a mixture of *Bacteroides*. (range—from 10^2 to 10^4 per gram of wet feces) and *Enterococci* (range—from 10^2 to 10^3), as the microbial population, while the feces of one of these seven subjects contained a mixed population of *Aerobacter* (10^2 per gram) and *Enterococci* (10^2 per gram). The stools of the remaining three of the seven subjects who had also been maintained on the diet for periods varying from 3 to 10 weeks were contaminated by a small non-pathogenic yeast population (range—from 10^1 to 10^3 per gram of wet feces), but were otherwise sterile, i.e., the population of no species was as great as 10 per gram of wet feces. In this test, no significant increase in the yeast or mold population of any subject accompanied the depletion of other microbial populations. Among the seventeen subjects, nine of the subjects revealed no detectable non-pathogenic yeast, while the total of these microorganisms per gram of wet feces was 10^1 in three subjects, 10^2 in one subject, 10^3 in two subjects, and 10^4 in two subjects.

As was noted above, a major mechanism for the production of free ammonia in the body is the action of microbial flora in the gastrointestinal tract, especially in the lower bowel, on proteins, amino acids, cellular debris, and other nitrogeneous wastes. Normally, such ammonia is absorbed into the portal circulation and carried to the liver where it is converted to urea through a detoxification mechanism involving the Krebs-Henseleit urea cycle or other enzymatic processes. The urea thus formed is normally excreted from the body in the urine. In certain disease states such as Lannec's cirrhosis, ammonia may accumulate in the blood, either because the portal blood flow is shunted around the liver or because the hepatic cells, by virtue of impaired function, become deficient in their ability to carry out one or more steps in the

detoxification cycle. Elevated levels of blood ammonia will then ensue which may lead to syndromes characterized by lethargy, confusion, delerium, or coma. Not only have high ammonia levels been implicated as a factor in various liver diseases such as cirrhosis and hepatitis. but there is some evidence that elevated blood ammonia levels may also be a factor in the development of organic brain syndromes and other kinds of illnesses including mental diseases such as schizophrenia. Various attempts have been made in the past to lower blood ammonia levels of patients suffering from severe liver disease or impaired liver function in order to alleviate the untoward physiological responses associated with the blood ammonia levels. The approaches used clinically for the reduction of blood ammonia levels include restriction of the protein intake, which thereby limits the amount of nitrogen and nitrogeneous waste available for ammonia formation; antibiotic therapy to reduce the intestinal microflora which mediate the conversion of nitrogeneous materials to ammonia; the alteration of intestinal microflora populations through their replacement with other bacterial species; and the administration of arginine to accelerate the enzymatic processes in the liver responsible for the conversion of ammonia to urea. Each of these approaches has its disadvantages and accordingly an attempt to lower the blood ammonia level of subjects suffering from elevated blood ammonia levels was made by the administration of the non-residual dietary compositions according to the invention.

EXAMPLE 3.

· The subject under investigation exhibited an intestinal microfloral pattern comprised predominantly of *Corynebacteriaceae* in addition of other microbial types. The subject also exhibited a sustained level of 1.6 micrograms of ammonia per milliliter of blood. He was confined to the non-residual diet of Table II for a period of 18 days. The subject ingested the diet at a rate sufficient to meet his subjective needs which averaged approximately 1500 calories per day. Within a short period of time on the diet, the subject's blood ammonia level dropped about 30% to approximately 1.1 micrograms ammonia per milliliter of blood and then stabilized in the range of 1.2 to 1.4 within the course of one week on the diet. The subject's ammonia level remained in this range for the remainder of the 18 days on the dietary regimen. At the end of the 18 day period, the subject was fed a diet of Lactinex and yogurt, followed by natural foodstuffs. The intestinal flora pattern of the subject showed no detectable amounts of *Corynebacteriaceae* either immediately after the end of the diet period or subsequently thereafter for an observation period of six months on natural foods. That a decrease in blood ammonia levels was accompanied by a corresponding decrease in the level of *Corynebacteriaceae* is shown in Figure 2. The blood ammonia level was found to be within the new baseline range upon determination some six months later.

EXAMPLE 4.

A subject suffering from liver disease due to chronic alcoholism exhibited symptoms ranging from mental confusion to a comatose state. His blood ammonia level was typically 1.6 micrograms per milliliter of blood on natural foodstuffs. During a period of two weeks just prior to the institution of feeding with the non-residual dietary composition according to the invention, he exhibited behavior ranging from coma - or lethargy to belligerence requiring confinement in a psychiatric ward. During the last mentioned period, he remained in bed, dozed or slept most of the time and at very sparingly. It was at this stage he was placed on the non-residual dietary composition of Table II for a one month period. After only three days on the non-residual diet, his blood ammonia level dropped to 0.7 micrograms per milliliter. A new baseline range of 0.7 to 1.2 micrograms per milliliter was established at the end of the one month course of non-residual diet feeding In addition, an indication of appreciable restoration of liver function during the one month course of feeding with the composition was manifested in blood protein data which showed increased serum albumin from a subnormal level of 2.7 grams per 100 milliliters to a normal level of 4.0 grams per 100 milliliters, normal range being 3.5 to 5.0 grams per 100 milliliters. The subject's albumin-globulin ratio increased during the same period from about 0.8 to 1.6, normal range being 1.2 to 1.7.

From the reduction in gut microflora which accompanies ingestion of the non-residual dietary compositions of this invention, it follows that such dietary compositions will be of utility in clinical states involving invasion of the intestine by parasites other than bacteria but which are dependent upon the presence of bacteria for survival. Amoeba is such a parasite. Thus a therapy for disease states such as amoebic dysentery (amebiasis) could include feeding the instant non-residual dietary compositions as the sole source of dietary sustenance for a period of time concomitant with the reduction of bacteria in the intestine to a level below the minimum required for survival of said amoebae. It is estimated that the desired clinical state would be reached within three weeks after initiation of the non-residual diet regimen. This process may be expedited through the use of a suitable purgative such as castor oil taken either just prior to the initiation of the non-residual diet regimen of after one day on said regimen.

The above examples are illustrative of the marked reduction in the quantity and type of intestinal microflora that occurs as a result of the continued ingestion of the non-residual dietary compositions and also illustrates certain beneficial side effects that occur as a result of the elimination of undesirable bacteria from the intestinal tract. While not wishing to be limited to the specific mechanism which will be described below, it is believed that the following mechanism may account for the effects herein described. The continued exclusive ingestion of the non-residual chemical diet apparently produces a complete elimination of bulk and undigested residues from the small and large intestines, thereby removing the loci for the support of and nutrient required for the growth of bacteria. The elimination of the bulk and undigested residue may be accomplished by this diet through the complete digestion and absorption of the dietary components of the diet in the upper portion of the gastrointestinal tract, the absence of bulk and indigestible materials in the diet and the promotion of clearance of existing bulk and other undigestible residues from the small and large bowels through what is tantamount to a flushing action.

The foregoing examples are illustrative of the effect of the non-residual diets on the intestinal microflora and also are illustrative of the certain desirable side effects which can be obtained by the elimination of intestinal microbes which may be undesirable themselves or undesirable because they constitute the food for other undesirable parasites. As was originally pointed out, the non-residual dietary compositions have general utility in such areas as the preparation of individuals for intestinal surgery and are useful in any area in which it may be desirable to alter or reduce the level of the intestinal microflora. The combination of the chemical non-residual diet regimen followed by replacement with other strains of bacteria provides an advantageous method for establishing desirable bacterial patterns in the intestines.

It should be noted that whereas the non-residual dietary composition is usually provided in a sterilized or pasteurized form to permit extended shelf life, the compositions need not be sterilized or pasteurized to produce the results and advantages described herein.

WHAT WE CLAIM IS:—

1. A nutritionably-adequate, non-residual dietary composition for mixing with water prior to consumption, which composition comprises a water-soluble component and a fat-soluble component; the water-soluble component comprising one or more water-soluble carbohydrates together with vitamins, minerals and, as sources of nitrogen, amino acids, amino acid derivatives, protein hydrolysates or mixtures thereof, the carbohydrate providing the major proportion (calculated as dry solids weight) of the said composition; and the fat-soluble component comprising one or more fat-soluble vitamins together with a small but nutritionally-adequate amount of fat, fat substitute or fatty acid or mixtures thereof; the ingredients of the said composition being such as to provide in use a nutritionally-adequate diet serving to reduce intestinal microflora levels.

2. A composition as claimed in claim 1 in which the water-soluble component includes a non-toxic emulsifier.

3. A composition as claimed in claim 2 in which the non-toxic emulsifier comprises polyoxyethylene sorbitan monooleate.

4. A composition for oral consumption which comprises an emulsion in water of a nutritionally-adequate, non-residual dietary composition as claimed in claim 2 or claim 3.

5. A composition as claimed in any of the preceding claims which contains a food colouring agent and/or artificial flavouring agent.

6. A composition as claimed in any of the preceding claims in which the carbohydrate comprises glucose.

7. A composition as claimed in any of the preceding claims in which the fat soluble component includes a mono-, di- or triglyceride.

8. A composition as claimed in any of the preceding claims in which the fat soluble component includes ethyl linoleate.

9. A composition as claimed in any of the preceding claims in which the minerals comprise salts containing sodium, potassium, magnesium, calcium, zinc, ammonium, cobaltous, manganous or ferrous ions.

10. A composition as claimed in any of the preceding claims in which the source of nitrogen comprises a mixture of the laevo form of lysine monohydrochloride, leucine, isoleucine, valine, phenylalanine, arginine, monohydrochloride, histidine monohydrochloride monohydrate, alanine, aspartic acid, threonine, proline, glycine, serine, tyrosine ethyl ester monohydrochloride, glutamine, methionine, or tryptophan.

11. A composition as claimed in claim 1 substantially as herein described.

12. A nutritionally-adequate, non-residual dietary composition substantially as herein described in any of Tables I to III herein.

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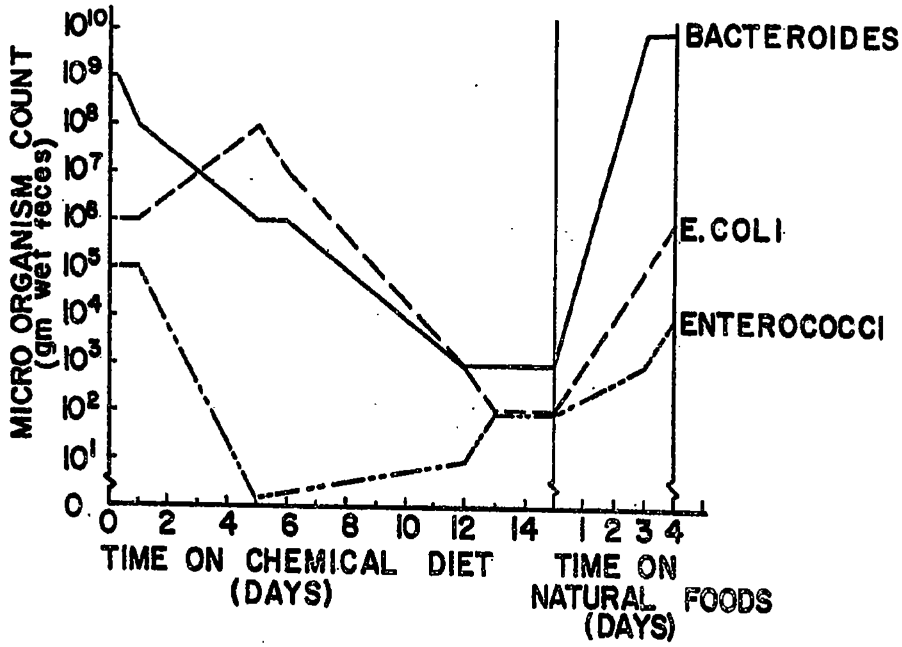

MICRO ORGANISM

	LOG COUNT		
	0 DAYS	15 DAYS*	+4 DAYS†
BACTEROIDES	9	3	10
E. COLI	6	2	6
LACTOBACILLI	6	-	3
CLOSTRIDIA	6	-	2
ENTEROCOCCI	5	2	4
STREPTOCOCCI	4	-	3
AEROBACTER	-	-	4
STAPH AUREUS	-	-	1
YEAST-LIKE FUNGI	4	-	2

* CHEMICAL DIET PERIOD
† NATURAL FOOD PERIOD

FIG. 1

1,159,615 COMPLETE SPECIFICATION
2 SHEETS
This drawing is a reproduction of the Original on a reduced scale.
SHEET 2

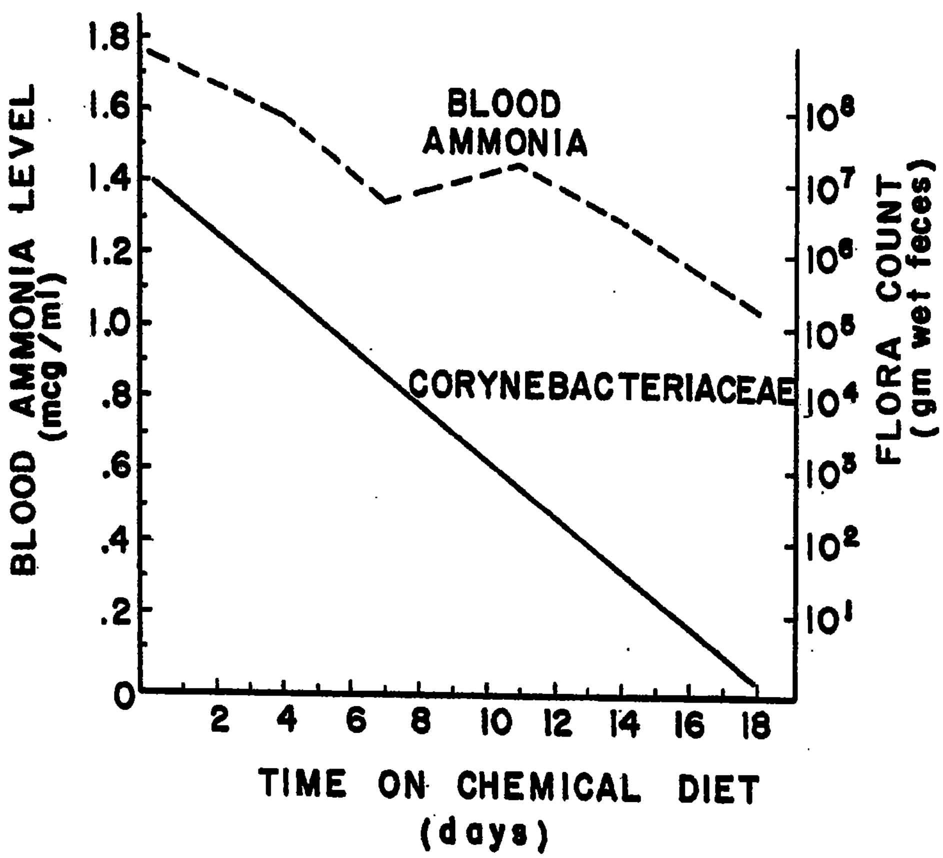

FIG. 2